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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/697,028
Filing Date: October 25, 2000
Appellant(s): OLSON ET AL.

Anita L. Meiklejohn
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on August 18, 2007 appealing from the Office action mailed 2/08/2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,326,145	WHITCOMBE et al.	12-2001

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 10-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Whitcombe et al. (USPN. 6,326,145).

Whitcombe et al. teach a method of claim 1, 16, for biasing (enriching desired nucleic acid) a DNA amplification reaction such that a first nuclei acid having a first nucleotide present at a polymorphic site (allele 1) is amplified to a greater extent than a second nucleic acid having a second, different nucleotide present at the polymorphic site (allele 2) (see col. 12, line 54-67, col. 13, line 1-52), said method comprising (a) contacting a sample of DNA with two amplification primers that hybridize to both the first and second nucleic acid molecule at locations that flank the polymorphic site, such that neither the first nor the second primer hybridizes to the polymorphic site (see col. 12, line 54-67, col. 13, line 1-20, col. 12, line 6-20, fig. 11 and 13, indicating opposing primers forward and reverse primers that flank a target sequence); one of the two primers including a 5' portion which, when incorporated into an amplification product, will upon further amplification yield products that form a stable-stem-loop structure (see col. 7, line 49-67, col. 8, line 1-11, col. 9, line 2-24, indicate stem-loop structures formed when scorpion primers are used, Figs. 9, 11-12, indicating stem loop structures), the stem of which is perfectly matched and includes the polymorphic site only when the second nucleotide is present at polymorphic site (allele-specific) (see col. 9, line 2-24, col. 10, line 53-67, col. 11, line 1-17, col. 13, line 45-52);

(b) carrying out amplification, whereby the first nucleic acid molecule is amplified to a greater extent than a second nucleic acid molecule (see col. 13, line 15-63, col. 16, line 20-34).

With regard to claim 16, Whitcombe et al. teach step (c) determining the nucleotide sequence of at least a portion of the DNA present in the amplified DNA sample (see col. 13, line 45-63);

With regard to claims 11-12, 14-15, Whitcombe et al. teach that the DNA comprises single-stranded or double-stranded derived from mammalian (human cells) such as blood, bacteriophage, viruses (see col. 6, line 1-10);

With regard to claim 13, Whitcombe et al. teach that the method further comprises separately carrying out steps (a) and (b) for each of a plurality of polymorphic sites (see col. 10, line 53-59, indicating two-tube (plurality) ARMS test). Accordingly Whitcombe et al. meets the limitations in the instant claims.

(10) Response to Argument

Introduction

The current claims are drawn to a method for biasing a DNA amplification reaction such that a first nucleic acid molecule having a first nucleotide at a polymorphic site is amplified to a greater extent than a second nucleic acid molecule having a second, different nucleotide present at the polymorphic site comprising contacting a sample of DNA comprising at least the first nucleic acid molecule with two amplification primers that hybridizes to both the first and second nucleic acid molecules which flank a polymorphic site, wherein neither of the primers hybridizes to the polymorphic site, one of the two primers including a 5' portion which when incorporated into an amplification product form a stable stem-loop structure, the stem of which is perfectly matched and includes the polymorphic site only when a second nucleotide is present at the polymorphic site; carrying out an amplification reaction, whereby the first nucleic acid molecule is amplified to a greater extent than the second nucleic acid molecule.

Anticipation

The anticipation is based on the prior art reference US Patent 6,326,145 (patent '145) to Whitcombe et al. The patent '145 discloses a DNA amplification method using tail primers that includes 5' portion (scorpion primers), which upon amplification get incorporated into the target nucleic acid forming a stable stem-loop structure. The amplification results in differential or biased amplification products, in which one target nucleic acid molecule having a nucleotide (mutant or variant) at the polymorphic site is amplified to a greater extent than the other target nucleic acid having a different nucleotide (wild-type or normal nucleotide) at the polymorphic site (col. 10, line 16-59, col. 12, line 54-67, col. 13, line 1-63). The amplification method comprises a real-time PCR monitoring amplification using a probe.

Appellants' analysis on the rejection under 35 U.S.C 102(e) and the arguments were fully considered and found unpersuasive. On page 5 of the Appeal Brief, Appellants argue that the '145 patent does not anticipate the present claims because it does not teach differential amplification required by the present claims. Appellants further assert that the '145 patent describes a detection probe that is capable of forming a stem-loop when a selected sequence is present in the sample and asserts that the patent teaches a Scorpion probe and not a primer for differential amplification. Appellants' arguments are unpersuasive. First, the amplification method is a differential amplification where the use of scorpion primers result in amplification of a mutant allele containing target nucleic acid to a greater extent than that of a normal allele (see example 1 on col. 12-13). Second, the patent '145 describes Scorpion primers having 5' tail portion, in addition to a detection probe, which is used in a real-time PCR to monitor the amplification. Thus the detection probe is used in the real-time PCR to monitor the amplification.

Third, the '145 patent does describe Scorpion primers (see at least abstract, col. 10, line 14-59) in addition to a detection probe to detect the amplification product in a real-time PCR format.

On page 6 of the appeal brief, Appellants' assert that the example 1 of the '145 patent cited by the examiner in the rejection, and the Fig. 13 of the patent disclose a probe (scorpion probe) that serves as a means for detecting a nucleic acid molecule and the fluorescence signal produced by probe that matched the target allele increased as the PCR amplification reaction increased the amount of template DNA in the reaction. Appellants' also assert that Example 1 of the patent '145 does not disclose differential amplification or do not suggest that two alleles were present in the reaction in Example 1. Appellants' arguments were fully considered and found unpersuasive. First, Appellants correctly pointed out that the probe serves as a means for detecting the nucleic acid molecule, however Appellants fail to address how the detection is achieved, that is, Appellants fail to address the amplification step of the detection process, which involves incorporation of scorpion primers into the primer extension product followed by monitoring amplification product in a real-time PCR format using a detection probe. The patent '145 is mainly concerned with scorpion primers, which are capable of forming hairpin loops when incorporated into the amplification product. Second, the example 1 does teach the use of scorpion primers for allele discrimination which clearly indicates hairpin forming regions of the primers form stable stem-loop depending on the allele present in the sample DNA and the probes are used in quantitating the alleles (normal vs. mutant allele) in a real-time PCR format. Third, the Example 1 clearly teaches presence of two alleles (normal and mutant allele) in template DNA (see col. 13, line 4-8) and does indicate the incorporation of scorpion primers into the amplicon that are detected by the probes targeted to these alleles. Fig 11 of the patent '145 shows

scorpion primers in allele discrimination and Fig 12 and 13 shows detection system involving a probe in monitoring amplification in a real-time PCR format. Thus the patent '145 does disclose differential amplification. In addition, the instant claims are in "comprising" open language format and thus any additional step can be added. Thus the claims do not exclude the real-time PCR format of monitoring amplification reaction using detection probe signals.

On page 6 of the appeal brief, Appellants assert that the patent teaches just opposite of differential amplification. The example 2 of the '145 patent and Fig. 14 describe the use of two different scorpion probes and argue that probes were causing the differential amplification and the efficiency of the amplification would depend on the match/ mismatch probe used. Appellants' arguments were fully considered and found unpersuasive. Examiner agrees that the scorpion probes are used in detection system, however, the probe alone does not constitute the amplification reaction. The '145 patent's main invention is drawn to novel scorpion primers and their use in PCR. The scorpion primers used in Example 1 does incorporate into the amplicon and the detection of said primer extension products are monitored in a real-time situation using probes that match/mismatch said alleles in example 2. Thus the signal generated in the amplification process detects whether a mutant allele is present or a normal allele is present in the sample. Thus the detection probe hybridization is only a detection means to identify whether the primer is incorporated into the amplification product or not, where that signal is proportional to the amount of the target present in the sample. The amplification of the allele present (normal or mutant allele) in the DNA sample itself constitutes differential amplification. Therefore the '145 patent does disclose differential amplification does disclose monitoring said amplification using probe(s) in a real-time PCR format.

Further Appellants assert that the scorpion probes do not include a 5'portion that is incorporated into the amplification product, because said probes include a blocking moiety that prevents tail region (col. 2, line 54-67) and assert that the probes do not contain a 5' region that is incorporated into the amplification as required by the patent claims. Appellants' arguments are full considered and found not persuasive. Appellants' arguments are solely based on the detection probes of the patent '145 and silent with regard to the Scorpion primers, which are, involved the amplification process. The assertions drawn to a probe not including a 5' region is irrelevant to the present context because the probes are used only as a means for detecting the primer extension products in a real-time PCR format and not for incorporation and extension step of the amplification. Further the cited paragraph supports the primer design in amplification processes, wherein a linker or blocking moiety is used to prevent the primer extension, as opposed to the Appellants' arguments. Thus the disclosure of '145 patent does anticipate the instant claims.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

Conclusion

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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